

## General

### Guideline Title

Guidelines for the first line management of classical Hodgkin lymphoma.

### Bibliographic Source(s)

Follows GA, Ardeshtna KM, Barrington SF, Culligan DJ, Hoskin PJ, Linch D, Sadullah S, Williams MV, Wimperis JZ, The British Committee for Standards in Haematology. Guidelines for the first line management of classical Hodgkin lymphoma. Br J Haematol. 2014 Jul;166(1):34-49. [PubMed](#)

### Guideline Status

This is the current release of the guideline.

## Recommendations

### Major Recommendations

Definitions for the quality of the evidence (A–C) and strength of recommendations (strong [Grade 1], weak [Grade 2]) are given at the end of the "Major Recommendations" field.

#### Pre-treatment Evaluation

- Patients require pre-treatment blood evaluation including human immunodeficiency virus (HIV) serology (1A).
- Staging with contrast-enhanced computed tomography (CT) of the neck to pelvis is required (1A), although positron emission tomography (PET)/CT is preferable if clinically feasible (1B).
- Early stage patients should be classified as favourable or unfavourable (1A).
- Advanced stage patients should be assessed to define a Hasenclever/International Prognostic Score (IPS) (1A).
- For male patients, pre-treatment semen cryopreservation should be offered where possible (1A).
- For female patients, pre-treatment review of options with a fertility specialist should be considered (1A).

#### Management of Early Stage Disease

- Prognostic factors should be determined to allocate patients to favourable and unfavourable sub-groups (1A).
- Standard of care for patients with favourable early stage Hodgkin lymphoma (HL) is 2 x doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) and 20 Gy radiotherapy (RT) (1A).
- Standard of care for unfavourable early stage HL is 4 x ABVD and 30 Gy RT (1A).
- A treatment option for unfavourable early stage HL is 2 x escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine,

procarbazine, prednisone (BEACOPP) + 2 x ABVD and 30 Gy RT (1A).

- The decision to omit RT from the management of IA/IIA non-bulky patients should involve discussion with a radiation oncologist (1B) and patients choosing to omit RT need to be aware of the balance of risks between RT and additional cycles of chemotherapy (1B).
- RT should not normally be omitted in patients presenting with bulky disease (1B).
- Early stage patients treated without RT should receive at least 3 x ABVD (1B).
- Patients receiving bleomycin should be assessed carefully for signs and symptoms of pulmonary toxicity before each dose. A history of new or worsening dyspnoea or pulmonary crackles should lead to stopping of bleomycin until an alternative cause is identified (1B).

#### Management of Advanced Stage Disease

- Patients aged 16 to 60 with advanced stage HL should receive either 6 to 8 cycles of ABVD or 6 cycles of escalated BEACOPP (1A).
- The choice between ABVD and escalated BEACOPP will depend on a range of factors, particularly the patient's opinion on the toxicity/efficacy balance between the regimens (2B).
- Patients with a higher IPS are at higher risk of relapse, potentially supporting the use of escalated BEACOPP in this higher risk group, although there are no prospective trial data to support a specific IPS cut-off at which escalated BEACOPP may be advantageous (2B).
- Patients treated with escalated BEACOPP who achieve an end-of-treatment PET-negative remission do not require consolidation RT to residual tissue (1A).
- Patients treated with ABVD should be considered for RT to sites of original bulk or residual tissue >1.5 cm. It remains unclear whether RT can be safely omitted in ABVD patients who have residual tissue >1.5 cm on CT that is PET-negative (1A).
- Interim positron emission tomography (iPET2) is highly predictive of outcome in patients treated with ABVD (1A).
- It remains unclear how iPET2 positive patients are optimally managed in routine practice. Accepting the limitations of small published datasets, treatment intensification to escalated BEACOPP ± RT appears reasonable (2B).
- Patients who remain PET-positive on completion of therapy require biopsy assessment or close clinical/radiological surveillance for early progression (1B).
- Patients who develop progressive disease on therapy should be considered for treatment intensification with transplantation (1A).

#### Management of HL in Pregnancy

- Patients should be closely co-managed with a specialised obstetric/fetal medicine unit (1B).
- Staging investigations and response evaluation should be tailored to the clinical presentation with radiology input to minimise fetal radiation exposure (1C).
- Delaying commencement of chemotherapy until post-delivery would not be standard practice and should be done with caution (1C).
- ABVD is the regimen of choice unless specifically contraindicated (1B).
- Wherever possible, RT should be delayed until post-delivery (1B).

#### Management of HL in Elderly Patients

- Elderly patients should be formally assessed for fitness to receive combination chemotherapy with a co-morbidity assessment tool which should distinguish "frail" from "non-frail" patients (2B).
- Patients considered "frail" should not usually be offered conventional combination chemotherapy (2B).
- "Non-frail" patients should be offered combination chemotherapy and RT with the aim of achieving complete response (CR), which is associated with better survival (1B).
- Older patients receiving bleomycin must be followed very closely for symptoms and signs of bleomycin lung toxicity (1A).
- Guidance on therapy choice for "non-frail" patients is hampered by the lack of randomised trial data. Treatment with vinblastine, cyclophosphamide, prednisolone, procarbazine, etoposide, mitoxantrone (VEPEMB) or cyclophosphamide, vincristine, procarbazine, prednisone (COPP)/ABVD appears to have lower treatment-related mortality than ABVD or BEACOPP (2B).

#### PET/CT in HL

- PET/CT should be reported by PET/CT imaging specialists (1C).
- As pre-treatment staging with PET/CT will upstage a minority of patients and aid the interpretation of subsequent PET/CT, it is recommended when clinically feasible (1B).
- PET/CT response should be reported according to Deauville criteria (2B).
- By Deauville criteria, a score of 1 or 2 should be considered "negative" and 4 or 5 considered "positive". Deauville score 3 should be interpreted according to the clinical context but in many HL patients indicates a good prognosis with standard treatment (1B).
- Biopsy is advised prior to second-line therapy to confirm residual disease with score 4 or 5 where possible to exclude false positive uptake with fluorodeoxyglucose (FDG) (1B).

- The optimal management of iPET2-positive patients remains uncertain. Therefore at this time iPET2 remains desirable for ABVD-treated patients but cannot be mandated as a standard of care (2B).
- If a pre-treatment decision has been made to treat an early stage patient with RT following ABVD, then there is no clear role for interim PET/CT (1A).
- End-of-treatment PET/CT is recommended for all patients who have not achieved an interim PET negative remission as this may directly affect RT planning, biopsy considerations and follow-up strategy (1B).

#### Radiotherapy Strategies in HL

- The evidence for the role of RT in HL is based on involved field RT (IFRT) (1A).
- Reduced volume approaches, involved node (INRT) or involved site (ISRT) are under evaluation in current protocols (2B).
- The dose for favourable early stage disease should be 20 Gy and 30 Gy for all other patients (1A).

#### Follow-up, Late Effects and Survivorship

- Patients are usually followed with intermittent outpatient clinical review for 2 to 5 years following first-line therapy (2C).
- There is no proven role for routine surveillance CT or PET/CT imaging in patients who are otherwise well following first-line therapy (2B).
- HL patients should be made aware that they are at an increased lifetime risk of second neoplasms, cardiovascular and pulmonary disease and infertility (1A).
- Apart from the current breast cancer screening programme, there are no national cancer screening programmes tailored for HL survivors. Women treated with mediastinal RT before the age of 35 yrs should be offered entry into the breast cancer National Notification Risk Assessment and Screening programme (NRASP) (1A).
- Regular lifestyle advice should be offered to reduce the secondary neoplasms and cardiovascular risk. There should be complete avoidance of smoking and careful management of cardiovascular risks such as hypertension, diabetes mellitus and hyperlipidaemia (1B).
- Patients who have had RT to the neck and upper mediastinum should have regular thyroid function checks. Hypothyroidism can occur up to 30 years after RT (1A).
- Patients should receive irradiated blood products for life (1B).

#### Definitions:

##### Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

##### Strength of Recommendations

Strong (Grade 1): Strong recommendations (Grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as "recommend".

Weak (Grade 2): Where the magnitude of benefit or not is less certain a weaker Grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as "suggest".

#### Clinical Algorithm(s)

None provided

# Scope

## Disease/Condition(s)

Hodgkin lymphoma

## Guideline Category

Evaluation

Management

Treatment

## Clinical Specialty

Hematology

Internal Medicine

Oncology

Radiation Oncology

## Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

## Guideline Objective(s)

To provide healthcare professionals with clear guidance on the management of patients with classical Hodgkin lymphoma (HL)

## Target Population

Patients with classical Hodgkin lymphoma (HL)

## Interventions and Practices Considered

Pre-treatment Evaluation

1. Pre-treatment blood evaluation including human immunodeficiency virus (HIV) serology
2. Staging with contrast-enhanced computed tomography (CT) neck to pelvis
3. Staging with positron emission tomography (PET)/CT (preferred)
4. Classification of early stage patients as favourable or unfavourable
5. Determination of Hasenclever/International Prognostic Score (IPS) in advanced stage patients
6. Pre-treatment semen cryopreservation for male patients
7. Pre-treatment review of fertility options for female patients

1. Management of early stage disease
  - Determination of prognostic factors to allocate patients to favourable and unfavourable sub-groups.
  - Favourable early stage Hodgkin lymphoma (HL) therapy: 2 x doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) and 20 Gy radiotherapy (RT)
  - Unfavourable early stage HL therapy: 4 x ABVD and 30 Gy RT or 2 x escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP) + 2 x ABVD and 30 Gy RT
  - Omission of RT from management based on discussion with radiation oncologist and patient
  - Assessing for signs and symptoms of bleomycin-induced pulmonary toxicity
2. Management of advanced stage disease
  - ABVD (6 to 8 cycles)
  - Escalated BEACOPP (6 cycles)
  - Consolidation RT to sites of original bulk or residual tissue
  - Interim positron emission tomography (iPET2)
  - Biopsy assessment or close clinical/radiological surveillance for early progression
  - Treatment intensification with transplantation for progressive disease
3. Management of HL in pregnancy
  - Co-management with a specialised obstetric/fetal medicine unit
  - Minimisation of fetal radiation exposure (delaying RT until post-delivery)
  - Delaying commencement of chemotherapy until post-delivery (not standard practice)
  - ABVD (unless specifically contraindicated)
4. Management of HL in elderly patients
  - Assessment of frailty
  - Combination chemotherapy and RT for "non-frail" patients (do not offer to frail patients)
  - Assessment for symptoms and signs of bleomycin lung toxicity
  - Treatment with vinblastine, cyclophosphamide, prednisolone, procarbazine, etoposide, mitoxantrone (VEPEMB) or cyclophosphamide, vincristine, procarbazine, prednisone (COPP)/ABVD
5. Use of PET/CT in HL management
6. RT strategies in HL (involved field RT [IFRT], involved node RT [INRT] or involved site RT [ISRT], radiation dosage)
7. Follow-up strategies
  - Intermittent outpatient clinical review for 2 to 5 years
  - CT or PET/CT imaging in patients who are otherwise well following first-line therapy (not recommended)
  - Patient information concerning increased lifetime risk of second neoplasms, cardiovascular and pulmonary disease and infertility
  - Entry into the breast cancer National Notification Risk Assessment and Screening programme (NRASP)
  - Lifestyle advice (for reduction of secondary neoplasms and cardiovascular risk)
  - Regular thyroid function checks for patients who have received RT
  - Irradiated blood products for life

## Major Outcomes Considered

- Survival rates (overall, progression-free)
- Female infertility rates
- Complete response rate
- Morbidity and mortality
- Treatment-related toxicity

## Methodology

### Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

MEDLINE and EMBASE were searched systematically for publications in English from January 1990 to June 2013 using key words Hodgkin, Lymphoma, Treatment, Chemotherapy, Radiotherapy. References from relevant publications were also searched.

## Number of Source Documents

Not stated

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose–response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

## Methods Used to Analyze the Evidence

Systematic Review

## Description of the Methods Used to Analyze the Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to quote levels and grades of evidence (see the "Rating Scheme for the Strength of the Evidence" field).

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

The guideline group was selected to be representative of UK-based medical experts and patients' representatives. The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Haemato-Oncology Task Force of the British Committee for Standards in Haematology.

## Rating Scheme for the Strength of the Recommendations

### Strength of Recommendations

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## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

### External Peer Review

### Internal Peer Review

## Description of Method of Guideline Validation

The guideline was reviewed by a sounding board of approximately 50 United Kingdom (UK) haematologists, the British Committee for Standards in Haematology (BCSH) and comments incorporated where appropriate.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field.)

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

Appropriate first line management of classical Hodgkin lymphoma (HL)

### Potential Harms

- The potential risk to fetal development from chemotherapy is likely to be higher in the first trimester.
- Patients receiving bleomycin should be assessed carefully for signs and symptoms of pulmonary toxicity before each dose. Bleomycin toxicity ranges from a measured decrease in diffusion capacity, lung volumes and vital capacity, to pneumonitis with nonspecific patchy opacities to end stage pulmonary fibrosis. Early symptoms and signs are dyspnoea/dry cough and crackles which occur 1 to 9 months after starting treatment and should lead to immediate cessation of the drug until another cause has been identified.
- As there are longer term risks for patients treated with radiotherapy (RT), it is recognised that in some circumstances, clinicians and patients

may prefer to treat without, particularly as the majority of IA/IIA non-bulky patients will be cured with chemotherapy alone.

- Older patients are more likely to die from non-HL causes, including bleomycin lung toxicity, which was reported in 24% of patients over 60 treated within the North American intergroup trial E2496. Therapy-related toxicity has, therefore, made delivering the 'gold standard' chemotherapies, doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) and bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP), challenging, especially in the over 70s and the major randomised trials contain only small numbers of elderly patients.
- The five-point scale (5-PS) also referred to as the 'Deauville criteria', can be used to assess response during treatment (with an interim scan) and at the end of treatment. To avoid the risk of under-treatment, score 1 and score 2 were used to define a 'negative' scan in the RAPID study. To avoid the risk of over-treatment, scores 4 and 5 were used to define a 'positive' scan in the National Cancer Research Institute (NCRI) RATHL study and in the Italian HD0607 study and scores 1,2,3 to define a 'negative' scan) with initial reports suggesting satisfactory responses for patients treated on trial.
- A recent large collaborative British Cohort study found that combined modality treatment (CMT) carried a greater relative risk (RR) for secondary neoplasms than chemotherapy alone.
- Depending on the age at treatment and the extent of the radiation field, the 25-year cumulative risk of breast cancer in women treated in childhood or early adulthood with RT is approximately 10% to 33%, compared with a lifetime risk in the UK of 11%.
- Myocardial infarction (MI) has been particularly linked to mediastinal RT. Significant and independent increased risk of MI was identified for supradiaphragmatic RT, anthracyclines and vinca-alkaloids. The risk was particularly high for the ABVD regimen and the combination of supradiaphragmatic RT and vincristine without anthracyclines.
- Fertility preservation techniques can only be discussed on a case-by-case basis, involving fertility experts and oncologists who can judge the appropriateness of the techniques and the risks of delaying treatment.
- Interim positron emission tomography/computed tomography (PET/CT) scans should ideally be performed as long after the last chemotherapy administration as possible to avoid potential false positive uptake.

## Qualifying Statements

### Qualifying Statements

- While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology (BSH) nor the publishers accept any legal responsibility for the content of these guidelines.
- The guidance may not be appropriate for all patients with Hodgkin lymphoma (HL) and in all cases individual patient circumstances may dictate an alternative approach.

## Implementation of the Guideline

### Description of Implementation Strategy

An implementation strategy was not provided.

## Institute of Medicine (IOM) National Healthcare Quality Report Categories

### IOM Care Need

Getting Better

Living with Illness

### IOM Domain



Effectiveness

Patient-centeredness

## Identifying Information and Availability

### Bibliographic Source(s)

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### Adaptation

Not applicable: The guideline was not adapted from another source.

### Date Released

2014 Jul

### Guideline Developer(s)

British Committee for Standards in Haematology - Professional Association

### Source(s) of Funding

British Committee for Standards in Haematology

### Guideline Committee

British Committee for Standards in Haematology (BCSH) Writing Group

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### Financial Disclosures/Conflicts of Interest

The authors have no conflicts of interest to declare.

## Guideline Status

This is the current release of the guideline.

## Guideline Availability

Electronic copies: Available from the [British Journal of Haematology Web site](#) .

Print copies: Available from the British Committee for Standards in Haematology; Email: [bcsh@b-s-h.org.uk](mailto:bcsh@b-s-h.org.uk).

## Availability of Companion Documents

None available

## Patient Resources

None available

## NGC Status

This NGC summary was completed by ECRI Institute on April 30, 2014. The information was verified by the guideline developer on May 28, 2014.

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